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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09 804,700	03/13/2001	Robert D. Ladner	266/176	1989

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EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/30/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,700	LADNER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response to the office action (Paper No. 16) filed on March 18, 2003 has been entered and considered.

Response to Arguments

2. With reference to the restriction requirement, Examiner notes that the acknowledgement of Applicants' election *without* traverse was a typographical mistake in the previous office action. Applicants' arguments are fully considered and Applicants' election of Group I (claims 1-10) in the previous office action with traverse is acknowledged herein. Applicants' arguments based on specific patents to rejoin the claims in Groups II with Group I were addressed in the earlier office action. As requested, the election of Group I with traverse is acknowledged herein.

3. With reference to the rejection made in the previous office action under 35 USC 103(a), Applicants' arguments are fully considered and found persuasive. The rejection is withdrawn herein in view of the arguments and new grounds of rejection.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A. Claims 1, 5-7, and 9, rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (USPN. 5,962,246) in view of Lundquist et al. (J Biol. Chem., Vol. 272, No. 34, pp. 21408-21419, 1997).

Ladner et al. teach a method for determining if a test compound induces uracil misincorporation into DNA, wherein Ladner et al. teach that the method comprises (a) providing normal or wild type cells (resting or non-proliferative cells or differentiated cells), cells over expressing dUTPase (proliferating cells, or less differentiated tumor cells) (see column 11, lines 49-67, column 12, lines 1-25); exposing or treating the cells to an agent that directly or indirectly inhibits thymidylate metabolism (see column 12, lines 32-48); measuring cell growth or proliferation or vialbility or measuring incorporation of uracil (dUTP) or amount of dUTPase (see column 12, lines 26-48, column 10, lines 44-46); (d) and interpreting the measured features wherein presence or absence of uracil in DNA in each of the cell types is indicative of the test compound inducing uracil misincorporation into DNA (see column 12, lines 26-48). Ladner et al. also teach that the cells over expressing a dUTPase are selected from organism including humans, animals, plants, fungi, bacteria and viruses (see column 10, lines 22-30). However, Ladner et al. did not teach use of cell types overexpressing uracil-glycosylase (UNG^+) and nonfunctional or uracil-DNA glycosylase inhibitor (UNG^-) expressing cells.

Lundquist et al. teach a method for cloning and transforming cells (bacterial cells) which over express uracil-DNA glycosylase (Ung) and cells, which express uracil-DNA glycosylase

inhibitor protein Ugi (see page 21409, column 2, paragraph 4, page 21410, column 2, paragraph 2). Lundquist et al. also disclose the interaction or binding of Ung with Ugi and the ability of Ugi in inhibiting the Ung activity (see page 21408, column 1, abstract, page 21412, column 2, paragraph 1).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining uracil misincorporation into DNA as taught by Ladner et al. with the cells expressing uracil-DNA glycosylase as taught by Lundquist et al. to achieve expected advantage of developing a sensitive method for characterizing uracil misincorporation into DNA because Lundiquist et al. suggests that "to block uracil-DNA repair and protect the uracil-containing DNA from degradation, Ugi expression and its inhibitory activity on Ung plays a major role" (see page 21408, column 1, paragraph 1). An ordinary practitioner would have been motivated to combine the method of Ladner with the method of Lundquist et al. to enhance the sensitivity of the assay by incorporating the additional parameters to support the uracil misincorporation into DNA because the comparison of different parameters in different cells would result in a better profile for characterization of a test compound and its role in misincorporation of uracil into DNA.

B. Claims 2-4, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al. (USPN. 5,962,246) in view of Lundquist et al. (J Biol. Chem., Vol. 272, No. 34, pp. 21408-21419, 1997) as applied to claims 1, 5-7, 9 above, and further in view of (Pearlman et al. USPN. 6,322,991).

Ladner et al. teach a method for determining if a test compound induces uracil misincorporation into DNA, wherein Ladner et al. teach that the method comprises (a) providing

normal or wild type cells (resting or non-proliferative cells or differentiated cells), cells over expressing dUTPase (proliferating cells, or less differentiated tumor cells) (see column 11, lines 49-67, column 12, lines 1-25); exposing or treating the cells to an agent that directly or indirectly inhibits thymidylate metabolism (see column 12, lines 32-48); measuring cell growth or proliferation or vialbility or measuring incorporation of uracil (dUTP) or amount of dUTPase (see column 12, lines 26-48, column 10, lines 44-46); (d) and interpreting the measured features wherein presence or absence of uracil in DNA in each of the cell types is indicative of the test compound inducing uracil misincorporation into DNA (see column 12, lines 26-48). Ladner et al. also teach that the cells over expressing a dUTPase are selected from organism including humans, animals, plants, fungi, bacteria and viruses (see column 10, lines 22-30). However, Ladner et al. did not teach use of cell types overexpressing uracil-glycosylase (UNG^+) and nonfunctional or uracil-DNA glycosylase inhibitor (UNG^-) expressing cells.

Lundquist et al. teach a method for cloning and transforming cells (bacterial cells) which over express uracil-DNA glycosylase (Ung) and cells, which express uracil-DNA glycosylase inhibitor protein Ugi (see page 21409, column 2, paragraph 4, page 21410, column 2, paragraph 2). Lundquist et al. also disclose the interaction or binding of Ung with Ugi and the ability of Ugi in inhibiting the Ung activity (see page 21408, column 1, abstract, page 21412, column 2, paragraph 1). Neither Ladner et al. nor Lundquist teach use of yeast cells as host cells and the interaction of antifolate test compounds.

Pearlman et al. teach a method to screen for dUTPase inhibitors in organisms comprising Saccharomyces cerevisiae wherein Pearlman et al. teach that the method comprises replacing endogenous dUTpase enzyme encoding gene with a functionally complementing enzyme

encoding gene from other target organism (see column 3, lines 5-46, column 4, lines 4-19, lines 60-67). Pearlman et al. also disclose that the gene encoding dUTPase is selected from C. albucans, herpes simplex virus and human cells (see column 5, lines 1-3); high level inducible expression is facilitated by GAL1 promoter (see column 5, lines 16-17); compounds which specifically inhibit the target dUTPase will exhibit a DNA synthesis-arrest cell morphology (see column 5, lines 18-25); compounds include 5-flurocytosine, antifungal agents and antiviral agents (see column 6, lines 30-53, column 2, lines 5-50).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine a method of determining uracil misincorporation into DNA as taught by Ladner et al. with the cells expressing uracil-DNA glycosylase as taught by Lundquist et al. and target host cells as taught by Pearlman et al. to achieve expected advantage of developing a sensitive method for characterizing uracil misincorporation into DNA because Lundiquist et al. suggests that "to block uracil-DNA repair and protect the uracil-containing DNA from degradation, Ugi expression and its inhibitory activity on Ung plays a major role" (see page 21408, column 1, paragraph 1). Further Pearlman suggests, " host cells like S.cerevisiae, is a well characterized eukaryote with a short generation time, permitting one to obtain screening results relatively quickly" (see column 4, lines 4-8). An ordinary practitioner would have been motivated to combine the method of Ladner with the method of Lundquist et al. and Pearlman et al. to enhance the sensitivity of the assay and reduce screening time by incorporating the additional parameters to support the uracil misincorporation into DNA because the comparison of different parameters in different cell types of yeast would result in a better

profile for characterization of a test compound and its role in misincorporation of uracil into DNA in a relatively less processing time.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 703-305-1004. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-305-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
May 22, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER